2-tailed t-test $P = .74$, Figure 1A). Results depend on the type of transplant received, however, as MUD transplants showed a differential expression in serum uric acid levels between the two groups (2.64mg/dl for aGVHD+ vs. 2.18 for aGVHD-, $P = .047$, Figure 1B), while MRD transplants did not show a difference (2.97mg/dl for aGVHD+ vs. 2.98 for aGVHD-, $P = .95$, Figure 1C). Patients given rasburicase had a lower serum uric acid level compared to the control arm (0.213mg/dl vs. 3.04 for d-7 to -2; 1.20mg/dl vs. 2.85 over all days, $P < .0001$) as well as significantly less aGVHD (rasburicase: 22% vs. control: 48%, Fisher's exact test, $P = .033$). Lower serum uric acid level at the time of transplantation appears to be protective against the development of aGVHD among patients receiving matched unrelated donor transplants. Rasburicase, when administered during the conditioning, significantly lowers the serum uric acid level and appears to decrease aGVHD.

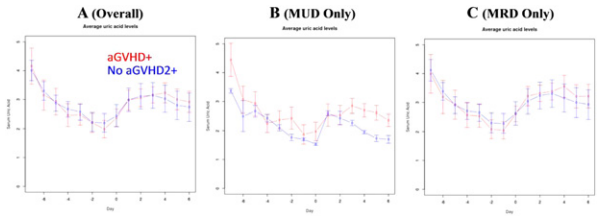

Figure 1. Mean uric acid levels from day-7 to day+6 between control patients who developed aGVHD2+ (Red) vs. no aGVHD2+ (Blue).

HEMATOPOIESIS/MESENCHYMAL CELLS ORAL

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Treatment of Steroid Resistant Grade II to IV Acute GVHD by Infusion of Mesenchymal Stroma Cells Expanded with Platelet Lysate - a Phase I/II Study

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Introduction: Despite improvements in the last decade in the field of HSCT, acute graft versus host disease (aGVHD) remains a life-threatening complication of HSCT. In particular, the outcome of patients with severe steroid-resistant aGVHD is very poor. Therefore, it remains important to search for new therapeutic strategies.
Objective: The feasibility of the generation of MSCs expanded with platelet lysate (PL) was tested as well as the feasibility and safety of the application in patients with steroid-refractory aGVHD. Immunological changes after infusion of MSC were characterized, in vitro. However, truly active mechanisms in human are poorly understood as well as whether infusion of MSC selectively impairs GVHD-inducing immune cells or also anti-virus and anti-leukemia reactive T-cells. Phenotypical and functional changes in immunological cell types and cytokine levels were investigated.
Method: In an open-label, non-randomized prospective phase I/II study MSCs from the bone marrow of healthy volunteers, expanded with PL. Patients with steroid-refractory aGVHD grade II-IV were treated with PL-MSC. 50 patients were included and received up to 4 infusions. Response rate, transplantation-related deaths, and other adverse events were assessed for up to 12 months after inclusion. In addition, a comprehensive phenotypical and functional analysis was performed with PBMCs and serum isolated from all patients before, during, and after infusion of MSC.
Results: Between 2009-2012, 50 patients were included, 2 dropped out, 5 are so far incompletely documented. Thus 43 were available for analysis, 6 children and 37 adults. Median age was 51,5 yr (1.3-65.9). Organs involved in aGVHD were skin (56%), gi-tract (86%) and liver (33%). Overall grade was II 26%, III 65%, and IV 7%. Mean number of infusion were 3 (1-4). No severe side effects were observed. Median follow-up was 4 months (0.4-12). Complete overall response was observed in 56% patients after a median of 53 days (3-116). The overall survival was significantly better in responders when compared to non-responders ($p < 0.001$). Immunological monitoring suggests that anti-viral and anti-leukemia reactive T-cells are well preserved in all patients who responded to MSC treatment. In addition, we identified biomarkers which associate even 2 weeks after MSC infusion with complete resolution of GVHD.
Conclusion: Generation and infusion of PL-MSCs in steroid-resistant aGVHD grade II- IV is feasible, safe and is effective. In addition, also patients who initially responded to PL-MSCs but develop later a relapse of aGVHD during tapering or cessation of immunosuppressive drugs become again sensitive to the treatment with steroids. Infusion of MSC did not impair anti-virus and anti-leukemia reactive T-cells. Identified biomarkers predict very early a usually late clinical resolution of GVHD, thus might be useful.

HISTOCOMPATIBILITY/ALTERNATIVE STEM CELL SOURCES ORAL

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Results of a Prospective Multi-Center Myeloablative Double-Unit Cord Blood Transplantation Trial in Adult Patients With Acute Leukemia and Myelodysplasia (submitted on behalf of the RCI BMT 05-DCB Protocol Team)

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Background: Retrospective studies suggest that double-unit cord blood (CB) grafts may improve engraftment and protect against relapse as compared with that observed after single-unit CB transplantation (CBT). However, whether the

promising disease-free survival (DFS) reported in single center series can be replicated in a multi-center setting has not been established.

Methods: We performed a prospective multi-center study of myeloablative double-unit CBT in adults. Eligible patients were 22-50 years and had acute leukemia in morphologic remission or MDS (<10% bone marrow blasts at work-up). CB grafts were 4-6/6 HLA-A,B antigen, -DRB1 allele matched to the recipient with a cryopreserved TNC $\geq$ 1.5 x 10^7/kg/unit and units were 3-6/6 HLA-matched to each other. Conditioning consisted of cyclophosphamide 120 mg/kg, fludarabine 75 mg/m^2, and total body irradiation 1320 cGy with cyclosporine-A and mycophenolate mofetil 1 gram every 12 hours as GVHD prophylaxis.

Results: Fifty-six patients [median 35 years (range 18-49), median weight 78 kg (range 53-127), and 33 (59%) CMV seropositive] were transplanted at 10 centers between 2007 and 2011. Thirty patients had AML (13 CR1, 17 CR2), 19 had ALL (11 CR1, 8 CR2), 4 had acute biphenotypic or undifferentiated leukemia (3 CR1, 1 CR2), and 3 had MDS. The median infused TNC doses were 2.9 x 10^7/kg and 2.1 x 10^7/kg for the larger and smaller units, respectively, and 4 (3%) units were 6/6, 40 (36%) 5/6, and 68 (61%) 4/6 HLA-matched to the recipient. The cumulative incidence of sustained donor neutrophil engraftment was 90% (95%CI: 82-96) at day 42 and 91% (95%CI: 82-97) at day 100 with a median time to neutrophil recovery of 22 days (range 13-94). Seventy percent (95%CI: 58-82) of patients had platelet recovery at day 180. The incidences of grade II-IV and III-IV acute graft-versus-host disease (GVHD) by day 100 were 66% (95%CI: 53-78) and 39% (95%CI: 27-52), respectively, and 21% (95%CI: 12-33) had chronic GVHD by 1-year. Day 180 transplant-related mortality (TRM) was 32% (95%CI: 21-45), and the 2-year relapse incidence was 10% (95%CI: 3-20). With a median follow-up of survivors of 24 months (range 11-26), 1-year and 2-year Kaplan-Meier estimates of DFS are 57% (95%CI: 44-70) and 50% (95%CI: 37-64), respectively. Of 26 patients who have died, 21 died of TRM which was most commonly due to GVHD (n = 9) followed by graft failure (n = 4), infection (n = 4), and organ failure (n = 4).

Conclusions: Double-unit CBT is a viable alternative treatment for high-risk acute leukemia and MDS, especially in those lacking a matched unrelated donor. However, our results highlight the need for further improvement in this therapy. The major challenges for patients were delayed or failed engraftment, infection, organ toxicity, and GVHD, whereas the relapse incidence was low. Strategies to further ameliorate the TRM after myeloablative double-unit CBT are needed.

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Donor-Recipient HLA-Matching of Unrelated Cord Blood (CB) Units At High-Resolution Reveals High Degrees of HLA-Mismatch and Alters Graft Selection

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Background: While CB units are traditionally matched to the recipient at HLA-A,B antigens & -DRB1 alleles with up to 2 mismatches permitted, significant associations between intermediate resolution HLA-C matching, & also HLA-A,B,DRB1 allele matching, & CB transplantation (CBT) outcomes have recently been reported. This suggests that CB donor-recipient match criteria should be upgraded to 6 HLA-alleles or higher. However, how to clinically implement higher resolution HLA-matching & its affect upon CB unit selection are unknown.

Methods: We analyzed the HLA-match grade of 96 double-unit CB grafts (units 1a & 1b) & the 1-2 back-up units chosen for each transplant at various match grades. 362 CB units were selected for 95 patients (1 patient was transplanted twice) who underwent CBT from 1/2009-6/2012 for hematologic malignancies. Units were selected based on cryopreserved TNC dose ($\geq$ 1.5, later increased to $\geq$ 2.0 x 10^7/kg), donor-recipient 4-6/6 HLA-A,B antigen, -DRB1 allele match & CB bank. Unit-unit match was not considered. High-resolution typing was obtained prospectively but usually did not influence unit selection.

Results: The median age was 41 years (range 1-69) & the median weight was 65 kgs (range 10-125). The median TNC/kg x 10^7 of units 1a & 1b (n = 192) was 2.89 (range 1.53-17.78), & their median donor-recipient HLA-match was 4/6 (range 1-6/6), 5/8 (range 2-8/8), & 6/10 (range 2-9/10) at 6, 8 & 10 HLA-alleles, respectively. The median (range) of 6/6 HLA-A,B antigen,-DRB1 allele matched units (n = 9) was 6/6 (3-6/6), 7/8 (5-8/8) & 9/10 (7-9/10) at 6, 8, & 10 allele resolution, respectively. However, 5/6 HLA-A,B antigen, -DRB1 allele matched units (n = 90) were a median (range) of 5/6 (2-5/6), 6/8 (3-7/8) & 7/10 (3-9/10) at allele resolution. Moreover, 4/6 HLA-A,B antigen, -DRB1 allele matched units (n = 93) were a median (range) of 3/6 (1-4/6), 4/8 (2-6/8) & 5/10 (2-8/10) at allele resolution. We then evaluated how often the use of higher resolution HLA-match criteria would change graft selection to substitute one or both back-up units over units 1a &/or 1b, & the effect on the graft TNC dose (Table). If a TNC/kg $\geq$ 2.0 x 10^7 & a better HLA-match were required, unit selection would change in 38/96 (40%) of transplants for 10 allele HLA-match. The effect on TNC was minimal ($\leq$ 12% reduction in the total graft TNC dose).

Conclusions: Units currently chosen based on HLA-A, B antigen, -DRB1 allele match have a very high degree of mismatch at higher resolution. Adoption of higher match grade criteria will frequently change the selection of the "optimal" graft. While the new lower limit of acceptable HLA-match & how to "trade off" higher resolution match against TNC dose are unknown, our data suggest that higher resolution HLA-match is frequently possible without significant compromise in graft dose.

Table

Match Grade	N (%) Grafts That Would Change	For Grafts That Would Change	
		Median (Range) Cryo. TNC: Original Choice for Graft (Larger/Smaller)	Median (Range) Cryo. TNC: New Choice Based on Higher Match Grade (Larger/Smaller)
6 allele: A, B, DRB1	26/96 (27%)	3.7 (2.1-12.0)/ 2.7 (1.9-6.6)	3.0 (2.0-8.0)/ 2.6 (2.0-6.6)
8 allele: A, B, C, DRB1	33/96 (34%)	3.6 (1.9-10.5)/ 2.7 (1.9-6.4)	3.2 (2.0-7.6)/ 2.5 (1.9-6.8)
10 allele: A, B, C, DRB1, DQ	38/96 (40%)	3.6 (2.1-10.5)/ 2.6 (1.6-6.4)	3.1 (2.0-8.7)/ 2.5 (1.6-7.6)